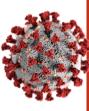
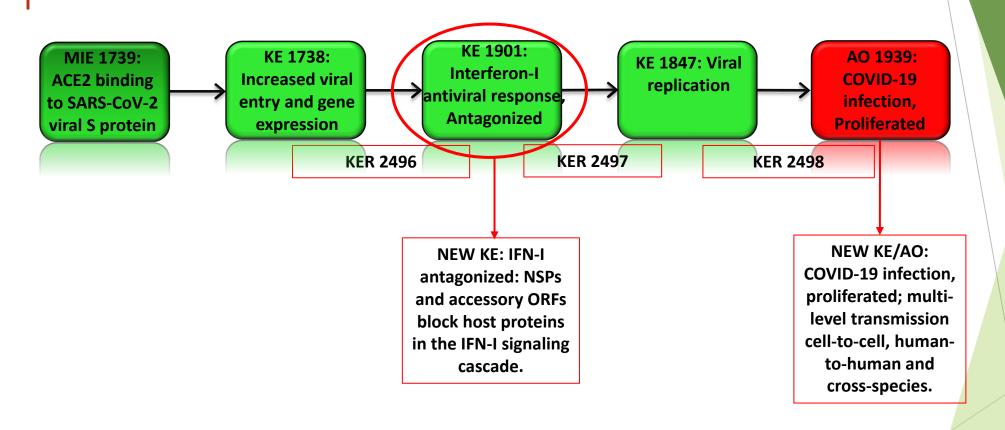
CIAO COVID AOP Early KE harmonization: SARS-CoV-2 entry and antagonism of Interferon (IFN)-I antiviral response leading to replication

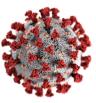
Sally Mayasich, Maria João Amorim, Laure-Alix Clerbaux, Penny Nymark, Julia Filipovska

CIAO COVID-19 5th Workshop, March 9-10, 2022

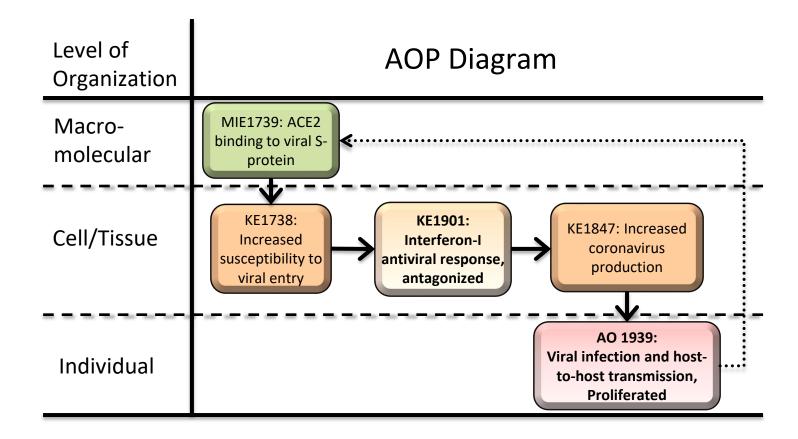


AOP 430: Sars-CoV-2 Interferon-I antiviral response antagonism and increased viral production leading to viral infection proliferation

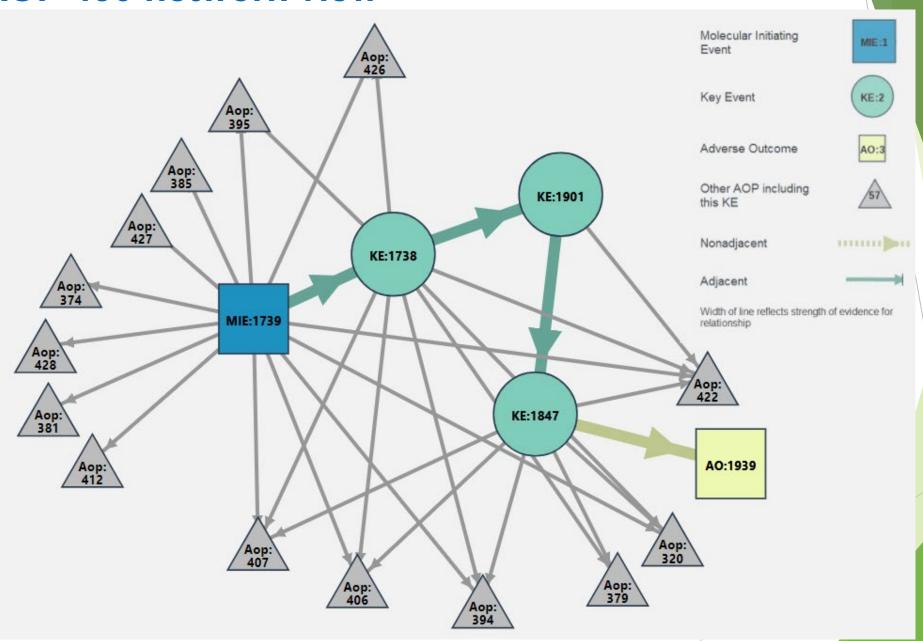




AOP 430: Sars-CoV-2 Interferon-I antiviral response antagonism and increased viral production leading to viral infection proliferation

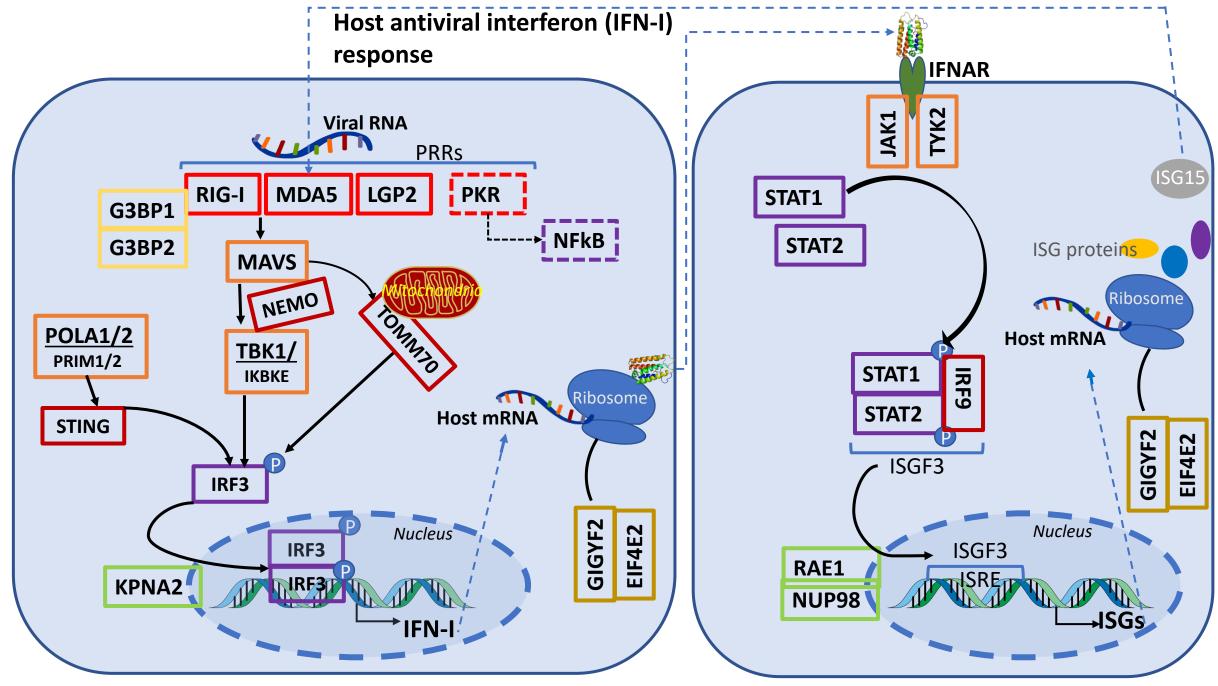


AOP 430 network view

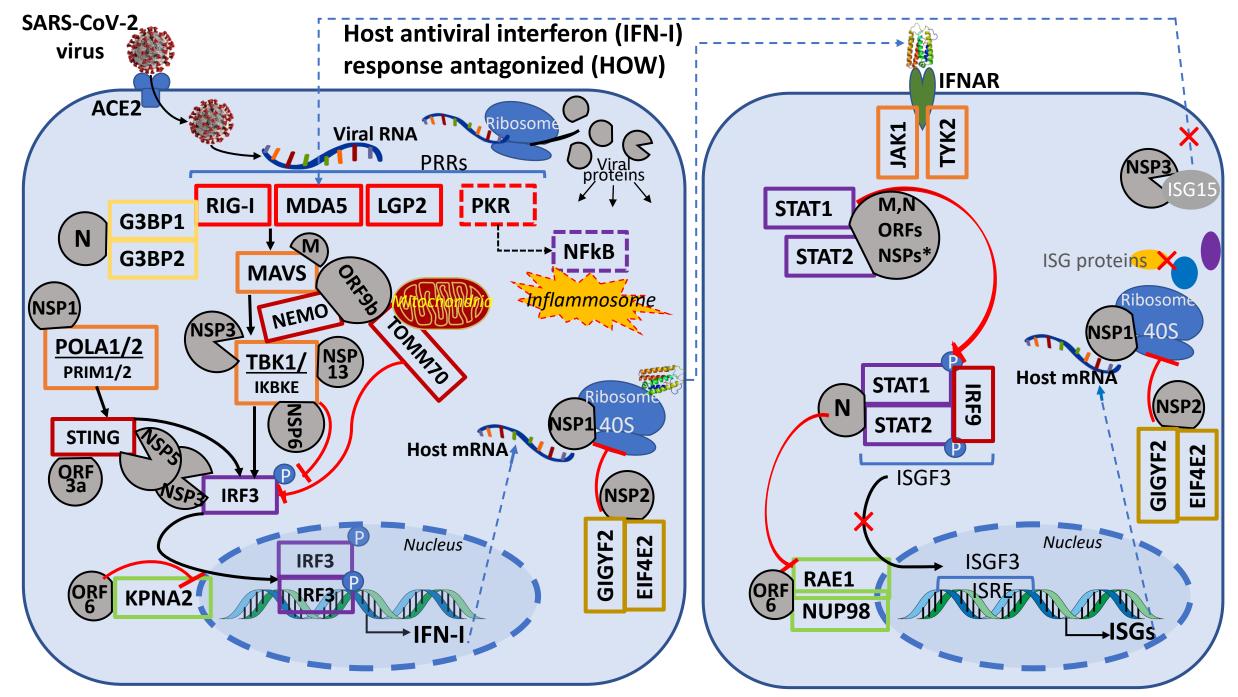


Failed viral detection Immune driven pathology Unsupervised Virus targeting of Virus inhibition complement Neutrophil of immune host restriction activation activation factors sensing Severe COVID-19 Tissue damage SARS-CoV-2 NK cell Viral suppression Inborn errors in Thrombosis Myeloid cytokines infection Organ failure dysfunction innate sensing of IFN Part 1 - Viral entry and evasion Part 2 - Dysregulated innate immunnity

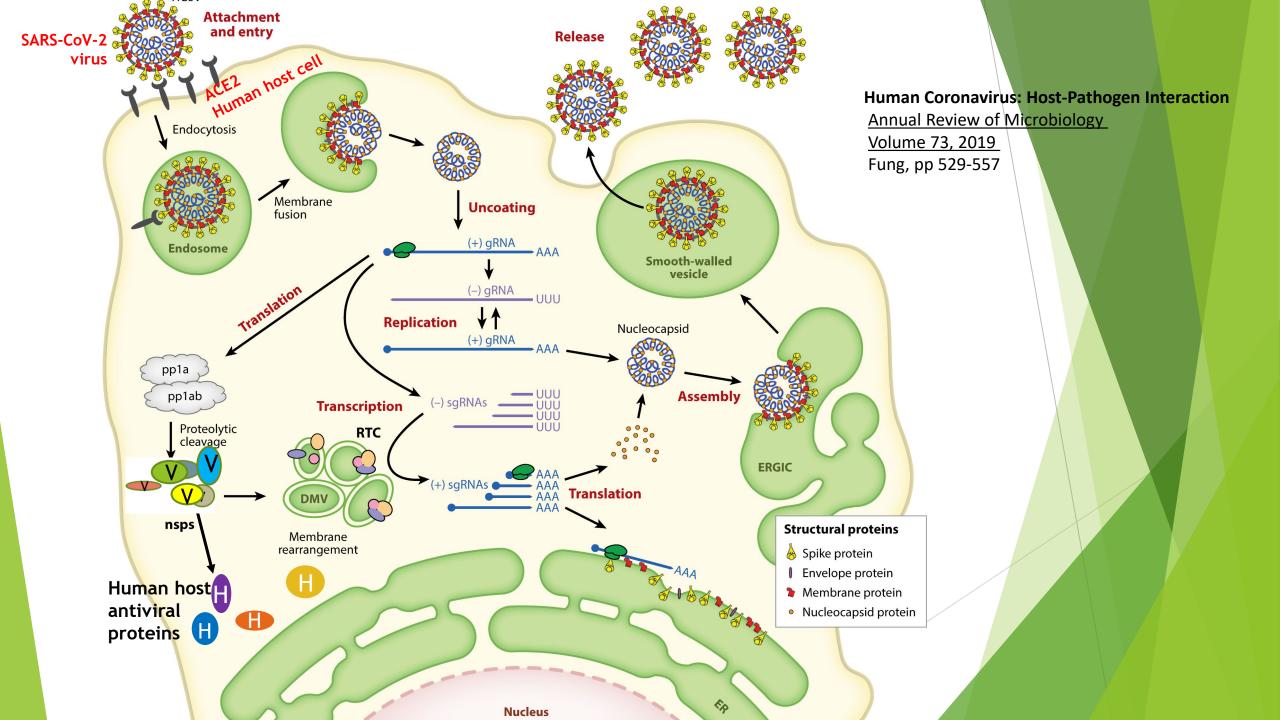
Innate immunology in COVID-19—a living review. Part I: viral entry, sensing and evasion Coveney et al. 2020 doi: 10.1093/oxfimm/iqaa004

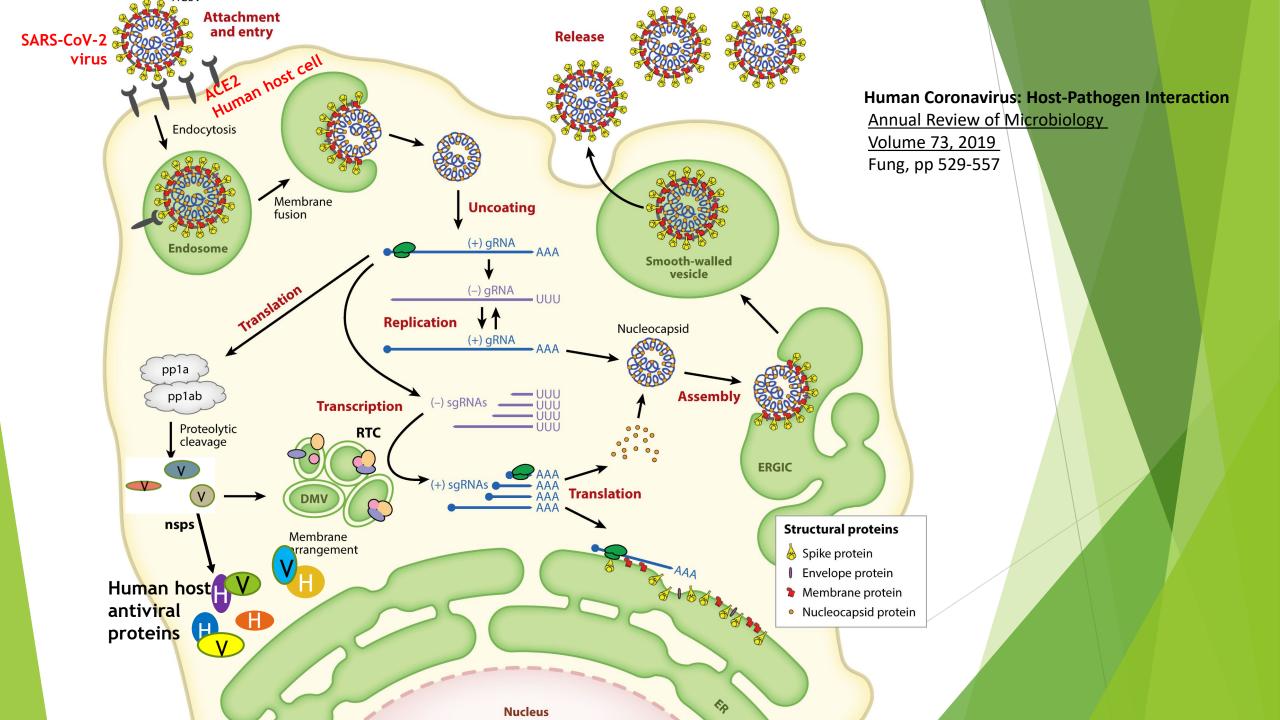


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Essentiality of IFN anti-viral response antagonism to downstream events

- ACE2 and TMPRSS2 proteins allow viral entry but are not the only determinant of viral replication
- ▶ IFNs are a key determinant in the progression of COVID-19.
 - ► Entry is essential for viral transcription → IFN antagonism → viral replication: viral load → disease/inflammatory responses and/or transmission.
 - ➤ Virus replication is prevalent in nasal, upper airway/lung, and enteric tissues that provide paths to distal organs and out of the body (to environmental exposure routes).

KER 2496: Increased susceptibility to viral entry (KE1738) *leads to* IFN-I response, antagonized.

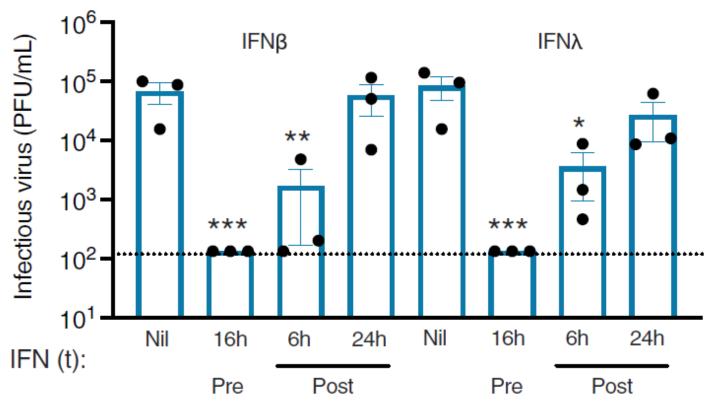
KE 1901: IFN-I response, antagonized

KER 2497: IFN-I response, antagonized leads to Increased SARS-CoV-2 production (KE1847).

- Biological plausibility
- Empirical evidence
 - ► Temporal concordance
 - Upstream: Dose/measured state
 - Downstream: Predicted/measurable response
- Uncertainties

IFN and Increased SARS-CoV-2 production Biological plausibility

- Interferon administered upon exposure abrogates viral production (Lopez, Madonov, Hatton, Hoaglund)
- ► IFN autoantibodies in some patients are an underlying factor for more severe disease (Bastard, Busnadiego)



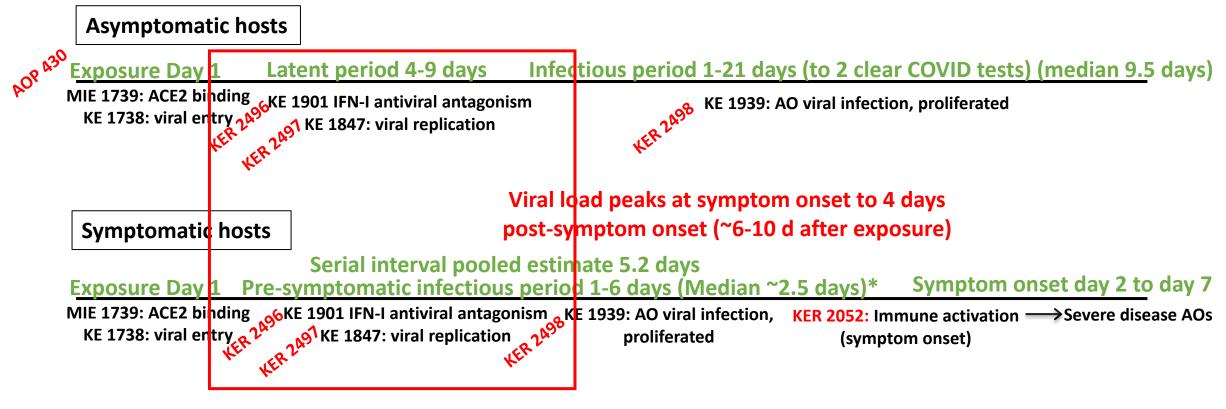
Exogenous IFN-I/III treatment controls SARS-CoV-2 replication. Nasal ALI cultures were either pre-treated (Pre) with IFN β (1000 IU/mL or IFN λ 1 100 ng/mL, for 16 h prior to infection with SARS-CoV-2, or IFN treatment was applied at 6 or 24 hpi (Post). Plaque assay on apical washes collected at 48 hpi. Dotted line indicates lower limit of assay detection.

Hatton et al. 2021 NATURE COMMUNICATIONS 12:7092 https://doi.org/10.1038/s41467-021-27318-0

IFN and Increased SARS-CoV-2 production Empirical evidence

- ► Empirical support for temporal concordance
 - Interferon expression delayed by SARS-CoV-2 vs. other viruses (Galani, Channappanavar)
 - Untuned/imbalanced response in moderate-to-severe cases (Galani, Blanco-Melo, Hadjaj, Hatton, Rouchka)
- ► IFN antagonism and viral replication/production may occur simultaneously but in separate cellular compartments
 - ► KE 1847 production is downstream based on essentiality:
 - \rightarrow if IFN is not antagonized (IFN \uparrow), viral production \downarrow (reduced/eliminated)
 - → IFN ↓, viral load

COVID-19 disease infectious period early stage timelines

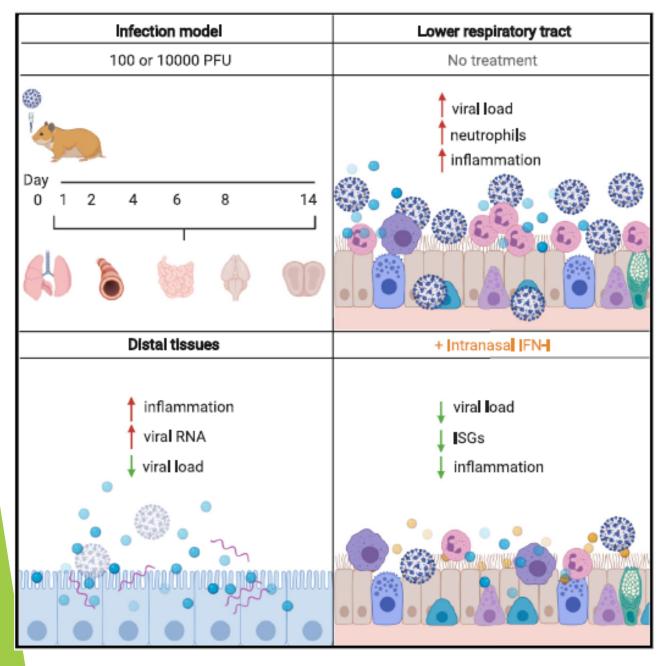


Serial interval: the time interval between the onset of symptoms in the primary and secondary case.

Latent period: period from exposure to infectiousness.

Serial interval 5.2 days – 2.5 days pre-symptom infectious period ≈ 2.7 days Latent period

The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of their institutions.



Hoaglund et al. 2021

Leveraging the antiviral type I interferon system as a first line of defense against SARS-CoV-2 pathogenicity Immunity 54, 557-570 doi.org/10.1016/j.immuni.2021.01.017

Highlights

- Infection and transmission can be initiated by respiratory or ocular exposure
- Systemic inflammation occurs despite little productive replication in distal tissues
- Intranasal IFN-I administered pre- or post-virus challenge reduces disease burden

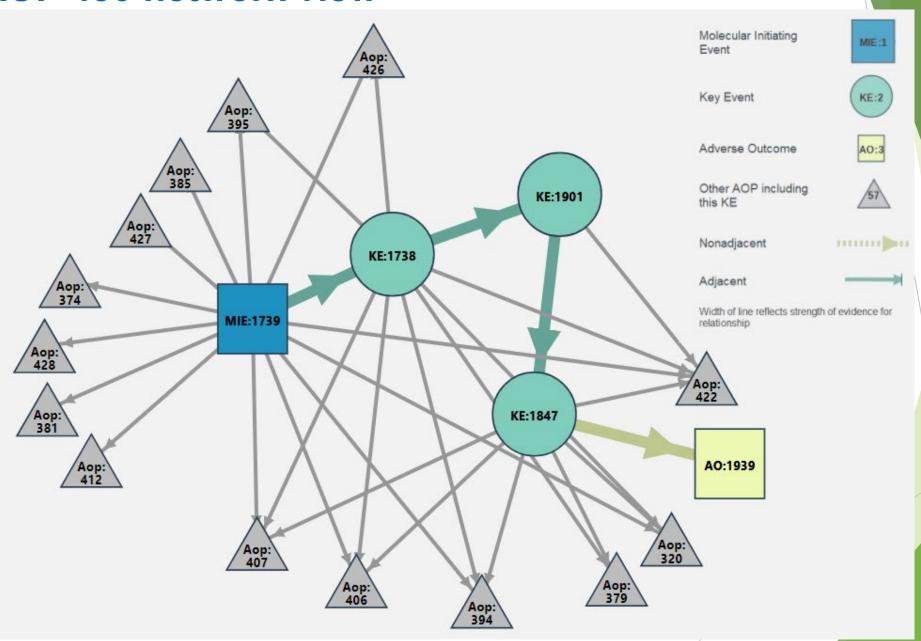
IFN and Increased SARS-CoV-2 production Cell and Tissue type specificity

- Tissues
 - ▶ Intestine Stanifer, Lamer
 - ► Nasal Hatton, Ahn
 - Lung Broggi
 - Upper airway Mick

AOP 430 network view

Molecular Initiating MIE:1 Event Pericytes possess a key role in the heart injury by COVID-19. Key Event KE:2 Sars-CoV/2 causes stroke Adverse Outcome Viral spike protein interaction with ACE2 leads to microvascular disfunction Other AOP including IFN-I response, antagonized this KE Downregulation of ACE2 causes multi-factorial heart injury and heart failure. Nonadjacent 111111111 Increased susceptibility to viral entry Adjacent Sars-CoV-2 causes encephalitis Width of line reflects strength of evidence for ACE2 binding to viral S-protein relationship ACE2 dysregulation leads to gut dysbiosis Enteric SARS-CoV-2 infection leads to intestinal hyperpermeability Increased SARS-CoV-2 production S glycoprotein, taste impairment SARS-CoV-2 infection leading to thromboinflammation Viral infection, proliferated ACE2 binding to viral S protein, Acute respiratory distress SARS-CoV2 to pyroptosis SARS-CoV2 to thrombosis and DIC SARS-CoV2 to hypekinflammation SARS-CoV-2 causes anosmia

AOP 430 network view



AOPs using MIE 1739, ACE2 binding to viral S-protein

Currently include KE 1738→KE 1847

- Viral replication required for downstream events:
- ► AOP 320
- ► AOP 379
- ► AOP 394
- ► AOP 406
- ► AOP 407
- ► AOP 422
- ► AOP 430: KE1738-KE1901-KE1847

Directly leading to adverse KE?

- No viral replication required?
- ► AOP 374 ? Brain cells neuroinflamation
- ► AOP 381 ACE2 downregulation
- AOP 385 ACE2 dysregulation
- ► AOP 395 ? Pericytes 1738→BBB disruption
- ► AOP 412 ACE2 inhibition
- ► AOP 426? Heart failure → 1738
- ► AOP 427 ACE2 downregulation
- ► AOP 428 ACE2 dysregulation

IFN and Increased SARS-CoV-2 production Discussion points

- Uncertainties: differing disease outcomes reported for interferon up- or downregulation and associated timing; different interferons
- Dosage: Initial vs. post-produced load
- ▶ Point of departure: Is KE after MIE 1739 (ACE2 binding to Spike protein) dose-dependent? Is replication required for ACE2 dysregulation?
- ► MIE 1739 as starting point? AOP 430 as "hub COVID MIE" module?
- Rules of AOP framework SARS-CoV-2 stressor or agnostic?